Rejection of Claims 26-30, 32, 33, 43, 52-54, 56-58 and 69-71 under 35 U.S.C. §112, first paragraph.

The Examiner rejects Claims 26-30, 32, 33, 43, 52-54, 56-58 and 69-71 under 35 U.S.C. §112, first paragraph for not being reasonably enabled by the specification (Page 2 of the present Office Action, as detailed on pages 3-8 of the previous Office Action dated May 10, 2001). The Examiner states, "while being enabled for the expression of the β_2AR gene *in vitro* in myocardiac cells by the transfection of the construct, and being enabling for the incresed rate of contraction of the transduced cells *in vitro*, [the specification] does not reasonably provide enablement for correction of cardiac dysfunction in mammals, and specifically in humans." (page 3 of the present Office Action) The Examiner further alludes to the "standard" with regard to claim breadth under 35 U.S.C. §112, first paragraph, which "entails the determination of what the claims recite and what the claims mean as a whole." (Page 3 of the present Office Action)

Applicants respectfully disagree with the Examiner's interpretation of the scope of Applicants' claimed invention. Applicants' further submit that the Specification provides support for regulation and altering cardiac rhythm *in vivo* as well as *ex vivo*.

It is axiomatic that claims are interpreted in light of the specification and that pending claims must be "given the broadest reasonable interpretation consistent with the specification." (MPEP §2111) However, it is also axiomatic that there is no need to resort to the specification to interpret the scope of a claim if the claim is clear on its face. *In re* Prater, 415 F.2d 1393 (CCPA 1969).

Appellants in *In re* Prater argued that, in light of the specification, their claimed invention was directed only to the patentable subject matter of a process performed by a machine. The Examiner of the Prater patent argued that, absent a specific limitation in the claim language, the additional limitations could not be read into the claims just because they were disclosed in the specification of the patent. The Appellant's argued that it was clear from the specification that the claims were directed to a process carried out by a machine. In Prater, the court in fact ruled that "'reading a claim in the light of the specification' to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim.'" (*In re* Prater, 1395) The court subsequently ruled that the appellants position required the court to read a limitation into the claim and not to merely interpret claim language. Because there was no explicit statement in the claim of such a limitation, the court found that the limitation could not be read into the claim.

Applicants submit that the present situation is analogous to the situation in Prater in that the Examiner does not point to any explicitly stated claim limitation that is unclear. The

Examiner insists that "the intended use of the claimed invention is directed to methods of treatment, and the specification has failed to provide a correlation to *therapeutic* levels of expression of the β_2AR gene in an *in vivo* setting in a subject suffering from, for example, cardiac conductive tissue incompetence." (page 4 of the present Office Action, emphasis in original) However, the claims clearly recite that the purpose of the methods are to upregulate heart rate or alter cardiac rhythm. Moreover, Applicants present data in the specification to demonstrate upregulation of heart rate and alteration of cardiac rhythm *in vivo*. The Examiner apparently ignores Applicants claimed invention and broadly confers subject matter in the specification that was not explicitly claimed. Although the claims must be read in light of the specification, the claim language must first be examined in order to determine which limitations, if any, need to be clarified (*Bell Communications*, 55 F.3d at 620, Fed.Cir.1995) In the present Office Action, the Examiner seeks to clarify language not explicitly recited in any of the claims. As there is no mention in the claims of a "therapeutic result," it is highly improper for the Examiner to import such language from the specification while interpreting the breadth of the claim. "If the claim language is clear on its face, then our consideration of the rest if the intrinsic evidence is restricted to determining if a deviation from the clear language of the claims is specified." (*Interactive Gift Express*, 256 F.2d at 1331, CAFC, 2001).

Although the PTO is not required to interpret the claims during prosecution in the same way a court would during an infringement suit, the MPEP states, "the PTO applies ***to verbiage*** of the proposed claims the broadest reasonable meaning ***of the words*** in their ordinary usage as they would be understood by one of ordinary skill in the art." (MPEP §2111, emphasis added) It is clear that the MPEP directs interpretation only of the claim language and subsequent examination of the claim based on the claim itself. For example, it is permissible for any patent applicant to disclose but not claim an aspect of an invention. It would be impermissible for the Examiner to reject the claimed invention based on, for example, art cited against the disclosed but not claimed invention merely because it is disclosed in the specification. Unless there is an explicitly stated question of interpretation of the claim language, MPEP §2111 does not give the Examiner license to import into a claim any possible limitation or expansion of scope just because it is mentioned in the specification but not actually claimed.

In the present case, the Examiner states that "the disclosed use of the claimed invention would be directed to therapeutic outcomes." (page 4 of the present Office Action) However, Applicants submit that this terminology appears nowhere in the claims and that the specification, in this case, is not being used to interpret claim language, but rather to impermissibly import subject matter not contained in the language of the claim. Instead, Applicants point out that the

methods of the claims are directed to "upregulating heart rate" and "altering cardiac rhythm." Applicants submit that an interpretation of these terms on their face twould not lead to an interpretation based on therapeutic effects.

The Examiner further rejects the claims as broadly reading on ***any*** mode of administration. For example, "claim 33, broadly reads on 'introducing' a biological pacemaker into the sinoatrial node of the mammalian heart...[The} claim is not limited to any particular mode of administration." (page 4 of the present Office Action) Applicants have amended Claim 33, which is drawn to " introducing a modified cell transfected or transduced with at least one gene that upregulates heart rate." A specific method is described- namely a method of cell grafting. As amended, Claim 33 is directed to introducing a specific type of biological pacemaker in a specific manner- by expressing a construct in cells that are placed in contact with a specific tissue. Applicants also provide support for methods involving direct injection of constructs into the sinoatrial chamber. Such methods avoid the unpredictability associated with gene therapy methods as cited by the Examiner and as argued previously in Applicants' Reply, dated July 12, 2000, to the previous Office Action (see the Reply, pages 6-8). As amended, the claims are directed to specific methods, *e.g.*, cell grafting and direct myocardial injection, of delivering specific biological pacemakers in order to regulate or alter cardiac rhythm.

The Examiner further rejects Applicants' argument that the disclosure of increased heart rate in the Yorkshire pig is not persuasive because, "[t]he Examiner notes that the Yorkshire pigs disclosed by the specification were not an art-recognized model for any disease involving cardiac conductive tissue incompetence." (page 5 of the present Office Action) Applicants direct the examiner's attention to MPEP §2164.02. "[T]he examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example." In light of Applicants' previous citation clearly establishing the Yorkshire pig as an art-recognized model for the human cardiovascular system (see the Reply to the previous Office Action, pages 8-9), and the complete lack of supporting evidence cited in the present Office Action to support the statement that the Yorkshire pig is not

an art-recognized model, Applicants submit that the data disclosed in the examples of the specification clearly enable the invention as claimed.

The Examiner states that the Specification is "enabling for the expression of the β_2AR gene *in vitro* in myocardiac cells by the transfection of the construct, and [is] enabling for the increased rate of contraction of the transduced cells *in vitro*." (page 2-3 of the present Office Action) Applicants submit that Claim 76, for example, is, by the Examiner's admission, enabled by the Specification.

In light of these remarks, Applicants submit that the Examiner is in error to import claim breadth not specifically claimed by the Applicants. In the absence of this improper reading of the claims, on their face, the claims are directed to specific methods for delivering specific compositions. The claimed methods are enabled through examples provided in the specification showing appropriate experiments using art-recognized animal models. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 26-30, 32, 33, 43, 52-54, 56-58 and 69-77 under 35 U.S.C. §112, second paragraph.

The Examiner rejects Claims 26-30, 32, 33, 43, 52-54, 56-58 and 69-77 under 35 U.S.C. §112, second paragraph "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (page 7 of the Office Action) In particular, the Examiner rejects the term "cellular-based" when referring to a cardiac biological pacemaker.

Applicants have canceled Claims 26, 28, 54, 56 and 58 and Claims 27, 29, 30, 32, 33, 43, 52, 57, 69, 70, 72, 73 and 76 have been amended to eliminate the use of the term "cellular-based". Claims 53, 71, 74, 75 and 77 depend on amended claims.

In light of the amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 26, 28, 29-31 and 43 under 35 U.S.C. §102

The Examiner has rejected Claims 26, 28, 29 and 43 under 35 U.S.C. §102(b) as being anticipated by Milano *et al.*, (Science, 1994, 264:582-586). The Examiner states "Milano *et al.* teach a construct that allows for the stable expression of β_2AR in the murine heart," and, further, that Applicants' "claims are directed to products, not methods." (page 8 of the Office Action) Applicants have canceled Claims 26 and 28, and have amended Claims 29 and 43 such that they

are now directed to methods. As amended, the teachings of Milano *et al.* do not anticipate amended Claims 29 and 43. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner has maintained rejections for Claims 26, 28, 30 and 43 and rejected Claims 76 and 77 under 35 U.S.C. §102(b) as being anticipated by Gaudin *et al.*, (J. Clin. Invest., 1995, 95:1676-1683). The teachings of Gaudin *et al.* have been described previously (page 9 of the previous Office Action). Applicants have canceled Claims 26 and 28, and have amended Claims 30 and 43 such that they are now directed to methods. Except for Claim 76, the claims have been amended and are directed to methods. Claim 76 is drawn to a composition, and, as amended, is directed to a cultured cell not taught by Gaudin *et al.* As such, the teachings of Gaudin *et al.* do not anticipate the claimed subject matter of Claim 76 or dependent Claim 77. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

27. (Amended) The method [cardiac pacemaker] of Claim 33 [26] wherein gene expression is localized to the sinoatrial node region of the right atria.

29. (Twice Amended) The method [cardiac pacemaker] of Claim 33 [26] wherein gene expression is regulated by at least one expression control element.

30. (Amended) The method [cardiac pacemaker] of Claim 29 wherein the expression control element directs transient expression.

32. The method [cardiac pacemaker] of Claim 33 [30] wherein the cell is isogenic, allogenic, or xenogenic.

33. (Amended) A method of upregulating heart rate [cardiac pacemaking activity] in a mammal by introducing a modified cell transfected or transduced with at least one gene that upregulates heart rate, said gene selected from the group consisting of: β_2AR, β_1AR and $G_{\alpha s}$, [biologic pacemaker according to Claim 26] into the sinoatrial node region of a mammalian heart, wherein the introduced cells express the gene in the cardiac tissue of the mammal resulting in an upregulated heart rate.

43. (Amended) The method [cardiac pacemaker] of Claim 29 wherein the expression control element directs stable expression.

45. (Amended) The method [cardiac pacemaker] of Claim 43 wherein the expression control element comprises an inducible promoter.

52. (Twice Amended) The method of Claim 33 wherein the [biological pacemaker is a cellular-based cardiac pacemaker construct comprising a] transfected or transduced

modified cell expressing a β2-adrenergic receptor [and] further [wherein the method] comprises *in vivo* administration of an adrenergic agonist.

57. (Amended) The method [cardiac pacemaker] of Claim 33 [56] wherein the modified cell is selected from the group consisting of: a myoblast, a cardiomyocyte, a skeletal muscle myoblast, a fetal or embryonic cardiomyocyte and a cardiac-derived cell line.

69. (Amended) A method of permanently upregulating heart rate [cardiac pacemaking activity] in a mammal by introducing [a cellular-based cardiac pacemaker comprising] at least one fetal or embryonic cardiomyocyte transfected or transduced with at least one gene that upregulates heart rate [or alters cardiac rhythm], said gene selected from the group consisting of: β_2AR, β_1AR and $G_{\alpha s}$.

70. (Twice Amended) A method of upregulating heart rate [cardiac pacemaking activity] in a mammal by introducing a [molecularly-mediated cardiac pacemaker] construct comprising at least one gene selected from the group consisting of:β_2AR, β_1AR and $G_{\alpha s}$ [that upregulates heart rate or alters cardiac rhythm], wherein said construct is suitable for localized stable gene expression in mammalian cardiac atrial tissue, and wherein said construct is introduced by direct myocardial injection or endocardiac transfection or transduction.

72. (Amended) The method of Claim 70, wherein the [cardiac pacemaker] construct is introduced into the sinoatrial node region of a mammalian heart.

73. (Amended) The method of Claim 70, wherein the [biological pacemaker is a molecular-mediated cardiac pacemaker construct comprising a gene encoding a β2-adrenergic receptor, and further wherein the] method further comprises *in vivo* administration of an adrenergic agonist.

76. (Amended) A cell in culture transduced or transfected with at least one gene that increases the rate of contraction of the cell.